extensively elsewhere are due to hypersensitivity to phenylbutazone in patients who have received this drug.

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Pemphigus foliaceus induced by penicillamine

Penicillamine is being used increasingly in the management of rheumatoid arthritis. It is the treatment of choice in Wilson's disease and cystinuria, but, as both of these disorders are rare, only relatively few patients have received the drug. Rashes occur in up to 60% of patients with Wilson's disease and cystinuria on penicillamine.[1-3] A much lower incidence is reported in rheumatoid arthritis (13-25%), possibly because smaller doses are given and the drug is introduced more cautiously.[4]

Morbilliform and urticarial eruptions are the most common lesions and they usually appear within the first 10 days of treatment. Withdrawing treatment leads to prompt recovery and the drug can usually be reintroduced without the rash recurring. Blistering and bruising with wrinkled scars and milia may occur on areas exposed to pressure and injury in patients with Wilson's disease or cystinuria, usually after the first year of treatment.[5 6] Such lesions, as well as elastosis perforans serpiginosa,[7] are probably related to penicillamine's lathyrogenic effects on connective tissues; they improve if the dose is reduced.

Rheumatologists are familiar with another "late eruption": raised, irregular, scaly plaques, which are extremely itchy and are mostly situated on the trunk.[4 8] They appear after about six months of treatment, are unresponsive to topical steroids, and take many weeks to disappear after the drug is discontinued.

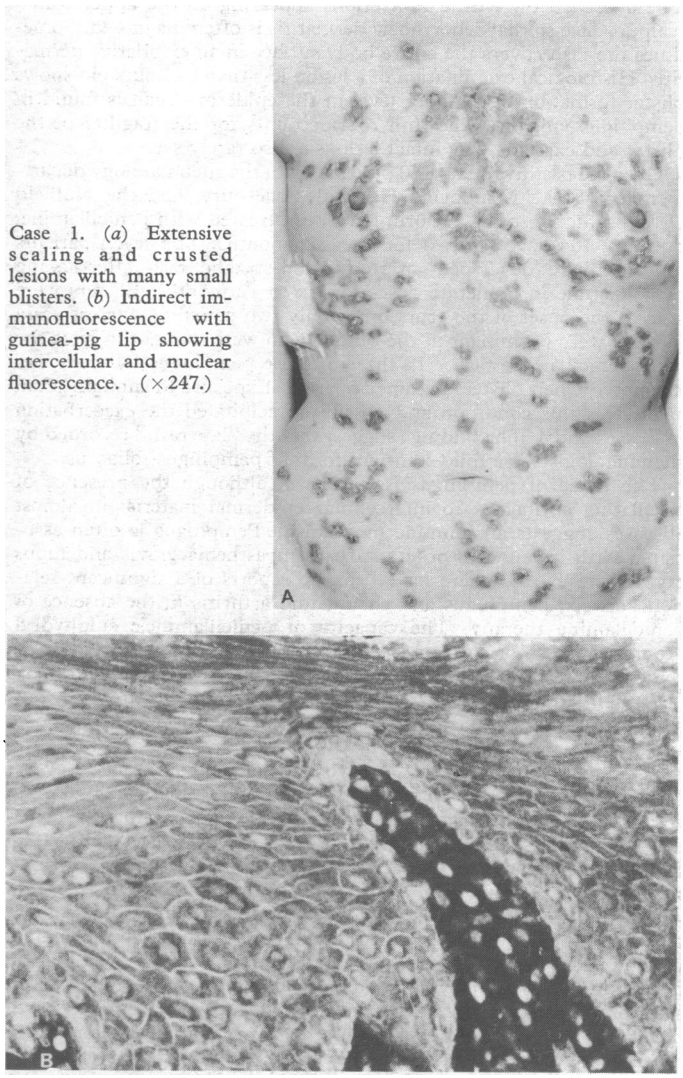
Pemphigus occurring during penicillamine treatment of Wilson's disease was first reported in France and later shown to occur in rheumatoid arthritis.[9-11] The patient may have pemphigus vulgaris or pemphigus foliaceus, and most improve when penicillamine is withdrawn. In some cases, however, the rash persists and is difficult to control. Since then this complication has become well recognised by British dermatologists.[12] We describe here seven patients who developed pemphigus.

Case reports

The two men and five women (aged 46-65), who had long-standing seropositive rheumatoid arthritis, poorly controlled by analgesics, prednisolone (in six cases), and gold (in four cases), were given penicillamine. In six the initial dose of penicillamine was 250 mg/day increasing by 250 mg each month to 750 mg/day; one patient received 500 mg/day throughout. After six to 12 months' treatment they complained of an itchy rash and the drug was discontinued

Case 1—A 46-year-old woman had scaly plaques, some with central or peripheral vesicles, on the abdomen. After five months numerous small blisters suddenly appeared (see figure). Skin biopsy showed subcorneal blister with moderate acantholysis and dermal perivascular infiltrate of lymphocytes and neutrophils. Serum epithelial antibody titre was 1/10, and she was positive for antinuclear factor (ANF) (IgG and IgM). The eruption has persisted for a year despite prednisolone and azathioprine.

Case 2—Erythematous lesions with marked peripheral scaling were first seen on the trunk in this 51-year-old man; four months later the eruption became extensive with blistering. Skin biopsy showed subcorneal blister, no acantholysis, and dermal perivascular infiltrate of neutrophils. Epithelial antibody titre was 1/10 and he was negative for ANF. The rash has been present for 23 months in spite of 20-30 mg prednisolone daily.



Case 1. (*a*) Extensive scaling and crusted lesions with many small blisters. (*b*) Indirect immunofluorescence with guinea-pig lip showing intercellular and nuclear fluorescence. (×247.)

Case 3—This 59-year-old woman had a few small blisters and scaly lesions on the trunk and scalp. Skin biopsy showed subcorneal blister, no acantholysis, and moderate perivascular infiltrate. She was negative for ANF. Epithelial antibody titre was 1/10, and smooth muscle antibody was present. Sepharose 6B filtration studies showed circulating IgG immune complexes. The rash, which has been present for five months, was improving with topical corticosteroids at the time of writing.

Case 4—This 65-year-old woman, who had severe digital vasculitis associated with rheumatoid arthritis, had several scaly lesions on the neck and later developed blisters. Skin biopsy showed epidermal ulceration and infiltration of the dermis by neutrophils. She was positive for ANF (IgM), and direct immunofluorescence of paralesional skin showed epidermal intercellular fluorescence. Four months after the lesions had healed with topical steroids the patient developed digital gangrene and penicillamine was restarted. The rash did not return although epithelial antibody was present in the serum (titre 1/10).

Cases 5, 6, and 7—Two patients had annular scaly lesions, while the third had small blisters which turned into crusts. Within eight weeks of stopping penicillamine all were free of lesions. Colour photographs were examined by dermatologists, who considered that the lesions were consistent with a diagnosis of pemphigus foliaceus. Penicillamine was reintroduced in one patient without recurrence of the rash, but the drug was finally withdrawn because of thrombocytopenia. Eighteen months later the patient died from Goodpasture's syndrome.

Comment

The term pemphigus refers to a group of uncommon blistering diseases which can affect all ages.[13] Pemphigus vulgaris, with its easily recognised blistering of the skin, is the best known. The much rarer pemphigus foliaceus is notoriously difficult to diagnose because blisters are not as obvious and leafy scales and crusts predominate.

The onset is slow with a few lesions appearing on the upper trunk, scalp, or face so that seborrhoeic dermatitis is often diagnosed. Sometimes the rash covers the entire body surface in an exfoliative dermatitis. Histological examination of a lesion less than 24 hours old shows blister formation at a higher level in the epidermis than is found in pemphigus vulgaris. The thin roof accounts for the fragility of the blister and explains why intact lesions are so rarely seen.

Over the past five years 160 patients from the rheumatology departments of Stoke Mandeville Hospital, Aylesbury, and the Nuffield Orthopaedic Hospital, Oxford, have been treated with penicillamine, but only 104 have taken it for over six months. The seven patients reported here developed an itchy, non-specific rash after taking penicillamine in moderate doses for six to 12 months. Blisters were seen at the onset of the eruption in only two patients, whereas scaly plaques were prominent in the others, who were thought to have the "late penicillamine rash." In three of these pemphigus foliaceus was diagnosed when blisters became apparent. Exposure to sunlight often aggravates this condition and possibly precipitated the exacerbation in cases 2 and 4. The findings suggest that the "late rash" recorded by rheumatologists is a mild transient form of pemphigus foliaceus.

The cause of pemphigus is unknown, although the presence of circulating antibodies to intercellular epidermal material in almost all cases suggests an immune mechanism. Pemphigus is often associated with immune disorders such as myasthenia gravis and lupus erythematosus, but there have been no reports of a significant relation between pemphigus and rheumatoid arthritis in the absence of penicillamine therapy. The capacity of penicillamine's sulphydryl group to bind to or cleave protein might alter epidermal intercellular cement substance, a proteoaminoglycan, with subsequent antibody formation. Reports of other drugs causing pemphigus are rare, but rifampicin, phenylbutazone, and Irgapyrin have been held responsible.[14 15]

Pemphigus foliaceus tends to have a prolonged course and may be fatal. The persistence of the rash in cases 1 and 2, 12 and 23 months after stopping penicillamine is therefore worrying. Although pemphigus foliaceus is less aggressive than pemphigus vulgaris, up to 60% of patients died of this disease before the introduction of corticosteroids; spontaneous remission occurred in about half of the survivors.[16] The prognosis has improved but 120-200 mg prednisolone daily may be required to control severe cases followed by maintenance doses usually over 30 mg/day. Many believe that even higher doses (up to 240 mg prednisolone daily) given for six to eight weeks are more likely to induce full remission, and cases 1 and 2 might have benefited from this more intensive regimen. Localised pemphigus foliaceus, as found in cases 3 and 4, is usually treated conservatively and may respond to topical corticosteroids alone.

Serum epithelial antibody titres in spontaneously occurring forms of pemphigus usually correlate well with the activity of the disease. In our patients, however, and those of Hewitt *et al*,[11] levels were low even though some patients had extensive lesions. Also of interest was the discovery of circulating epithelial antibody in case 4 about nine months after the rash had disappeared and penicillamine had been reintroduced. Further investigation is therefore required to explain these anomalies and to determine whether the antibody is found in the blood before the onset of the eruption.[17] Serial serum antibody estimations might be helpful in managing and preventing this serious disease.

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Prazosin treatment complicated by acute febrile polyarthritis

Prazosin (Hypovase) is a recently introduced hypotensive agent, which is said to act peripherally by direct vasodilatation.[1] Apart from collapse due to postural hypotension on starting treatment,[2] side effects have been trivial. We draw attention here to a further possible complication of prazosin treatment.

Case report

In 1969 a 32-year-old man developed intermittent claudication of the right calf. No pulses could be felt below the femoral artery in the right leg. An aortogram showed complete occlusion of the right popliteal artery. Two years later he was reinvestigated after developing a left popliteal artery aneurism. He had bruits over both subclavian and carotid arteries. The right leg pulses were still absent. His erythrocyte sedimentation rate was 30 mm in 1 h. Aortography showed, in addition to the aneurism, multiple stenoses in the head and arm vessels, left renal artery stenosis, and right popliteal artery occlusion. The aneurism was excised and examined histologically. No diagnostic pathological change was seen. A muscle biopsy specimen was normal. The patient remained well until six years later, when he was found to be hypertensive (blood pressure 180/120 mm Hg). An intravenous pyelogram and radioactive renograph confirmed the diagnosis of renal artery stenosis.

Treatment—He was started on prazosin 2 mg three times a day, and his blood pressure was controlled.

Adverse effects—Ten weeks later he began to complain of "flu-like" symptoms with soreness of the throat associated with shivering and sweating. He developed an ache in the neck and pain in the right groin and was admitted to hospital. On examination he was febrile (40°C). There was no lymphadenopathy or rash. The peripheral pulses were unchanged. His blood pressure was 180/110 mm Hg. Right hip and neck movements were full. The prazosin was stopped and by the next morning his temperature was normal. Twenty-four hours later he developed acute arthritis of the right elbow and both knees with a large effusion into the right elbow joint. This arthritis settled within 24 hours with aspirin treatment. On admission he had a neutrophil leucocytosis (white cell count $15 \times 10^9/l$(15 000/mm^3)) and a plasma viscosity of 2·00 centipoise. Urine examination, blood urea and electrolytes, liver function tests, and blood lipids were normal. The serum urate concentration was normal and latex fixation test and test for antinuclear factor gave negative results. Blood cultures grew no organisms, and antibody titres against brucella and rickettsia were normal. The Wassermann reaction was negative. Radiographs of the chest and affected joints showed no abnormalities.

The patient was well when seen again two weeks after discharge and his prazosin was restarted. Three days later his symptoms recurred and he